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Age as a Predictive Factor in Glioblastomas: Population-Based Study

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Key Words

Glioblastoma • Population-based study • Age • Radiotherapy • Survival

Abstract

We evaluated 715 glioblastoma patients diagnosed during 1980–1994 in the Canton of Zurich, Switzerland, to provide information on how patients were treated at the population level. Despite a general policy during the study period of treatment by surgical intervention aimed at maximum tumor removal followed by radiotherapy, there was a marked tendency toward limited treatment with advancing patient age. Of those younger than 65 years, 82% were treated either with surgery followed by radiotherapy, surgery alone or radiotherapy alone, versus 47% of patients 65 years or older. Only 25% of patients older than 75 years underwent surgery and/or radiotherapy, while the remaining patients were given best supportive care (BSC). The mean ages of patients were 54.5 years for those treated with surgery and radiotherapy, 58.3 years for surgery alone, 62.2 years for radiotherapy alone and 69.2 years for BSC. Among patients who were treated with surgery plus radiotherapy and those treated with radiotherapy alone, younger patients (<60 years) had a significantly higher survival rate than older patients (≥60 years). In contrast, no significant difference in survival was observed between younger and older patients treated with

surgery alone or receiving BSC, suggesting that lower survival rates in elderly patients with glioblastoma may be at least in part due to a lesser response to radiotherapy.

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Introduction

Glioblastoma is the most common and malignant brain tumor. Despite advances in surgery and clinical neuro-oncology, the outcome of glioblastoma patients is still very poor. Since the study by Walker et al. [1], which showed an increased survival of patients receiving radiotherapy after surgery compared to surgery alone, adjuvant radiotherapy became the standard first-line treatment for patients with glioblastoma in many countries. More recently, combined radio- and chemotherapy after surgical intervention has become a standard treatment for glioblastoma [2, 3]. A meta-analysis of 3,004 malignant glioma patients from 12 randomized controlled trials showed a modest but statistically significant prolongation of the 1-year survival rate (from 40 to 46%) and a 2-month increase in median survival time for adjuvant nitrosourea-based chemotherapy added to radiotherapy after surgical resection [2]. In a multicenter phase III trial, Stupp et al. [3] reported that glioblastoma patients treated with radiotherapy plus temozolomide had in-

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creased median overall survival times compared to patients treated with radiotherapy alone (14.6 vs. 12.1 months), with 1- and 2-year survival rates after temozolomide treatment being 61.1 and 26.5%, respectively [3]. However, as in most clinical trials, treatment was offered to only a selected subgroup of malignant glioma patients (i.e. younger than 70 years of age, good performance status, maximum surgical resection) [3]. So far, there has been little information on how glioblastoma patients are actually treated, and how different treatment options affect clinical outcome at a population level.

Previous clinical trials and hospital-based studies have repeatedly shown that patient age, performance status and extent of surgical resection are prognostic factors for the survival of glioblastoma patients [4, 5]. In particular, older age is the most significant and consistent factor prognostic of poor survival of glioblastoma patients [5–9]. Little is known about the mechanisms underlying this observation; however, since it has been reported in virtually all clinical trials irrespective of the specific therapy protocol examined, it is generally assumed to be due to an intrinsic change in the biology of glioblastomas of older patients rather than reflecting a different response to therapy.

The present study is a part of a population-based study on astrocytic and oligodendroglial gliomas in the Canton of Zürich, Switzerland, which we previously reported [8, 9]. In the present study, we have analyzed how glioblastoma patients were actually treated at the population level, and assessed the correlation between age and effect of treatment in 715 glioblastoma patients.

Patients and Methods

Glioblastoma Patients

This study includes 715 cases of glioblastoma (ICD-O 94403, 94413 and 94423) [10] diagnosed in the resident population of the Canton of Zürich, Switzerland (approx. 1.16 million) during the 15-year period from 1980 to 1994 [8, 9]. The majority of cases (571 cases, 79%) were histologically diagnosed following surgical resection (374 cases) or stereotactic biopsy (12 cases), or at autopsy (185 cases). The remaining 144 cases (21%) were clinically diagnosed by CT or MRI [8], typically based on the presence of an irregularly shaped lesion of contrast enhancement with a central area of necrosis and with perifocal edema [10]. Patients who underwent only stereotactic biopsy were not included in those treated by surgical intervention. Radiotherapy before histological glioblastoma diagnosis was carried out in only 5% of all patients (28 primary and 10 secondary glioblastomas).

The incidence date was fixed as the date of the pathology report for patients who underwent surgery or the date of clinical diagnosis. The survival time was computed as the period between

the incidence date and the date of death, the date of last contact if lost to follow-up, or April 2006. Follow-up was complete for 99% of the cases, with a mean follow-up time of 7.2 ± 7.6 months. Death certificates were collected in the Cantonal Cancer Registry [8]. Survival data were available for a total of 664 patients (239 cases treated with surgery and radiotherapy, 145 cases treated with surgery alone, 66 cases with radiotherapy alone and 214 cases treated with best supportive care). The mean age of all patients was 61.3 ± 14.0 years; 402 (56%) were men (mean age 61.0 ± 13.3 years) and 313 (44%) were women (mean age 61.7 ± 14.8 years).

Statistical Analyses

The logrank (Mantel-Cox) test was used for comparing survival curves. Scheffé's method was applied to multiple comparisons (post-hoc test) of mean ages of patients among the different treatment options. Statistical analyses were performed with StatView for Windows 5.01 (SAS, Cary, N.C., USA) and with SAS. Multivariate Cox regression models were used to assess predictive values of different treatments on patient survival. Adjustments were made for age, gender and treatment.

Results

How Glioblastoma Patients Were Treated at the Population Level

The general policy of treatment of glioblastoma at the University Hospital Zürich between 1980 and 1994 was surgical intervention aimed at maximum tumor removal, followed by radiotherapy. Radiotherapy typically consisted of 2 Gy fractions, with a cumulative dose of 60 Gy, except for 13 patients who were irradiated with a lower dose (range: 6–50 Gy). Adjuvant chemotherapy was not given to any of the patients during the study period.

Of 715 cases of glioblastomas, only 239 cases (33%) underwent surgical intervention followed by radiotherapy, while 147 cases (21%) had surgery alone, 77 cases (11%) had radiotherapy alone and 252 cases (35%) received only best supportive case care (BSC; i.e. neither surgical resection nor radiotherapy).

Survival of glioblastoma patients treated with surgery plus radiotherapy was significantly longer (median: 10.1 months) than those treated with surgery alone (4.3 months), radiotherapy alone (4.1 months) or patients receiving BSC (1.9 months); logrank test $p < 0.0001$.

Of patients younger than 65 years, 82% were treated either with surgery followed by radiotherapy, surgery alone or radiotherapy alone, versus 47% of patients 65 years or older. Only 25% of patients older than 75 years underwent surgery or radiotherapy, while the remaining patients were given BSC (fig. 1). The mean age of patients treated with surgery and radiotherapy was 54.5 years, significantly younger than those treated with surgery alone

Fig. 1. Treatment options among different age groups of glioblastoma patients. The majority of patients younger than 54 years were treated with surgery and/or radiotherapy, whereas older patients were less frequently treated with surgery or radiotherapy. Only 25% of patients older than 75 years received surgery and/or radiotherapy.

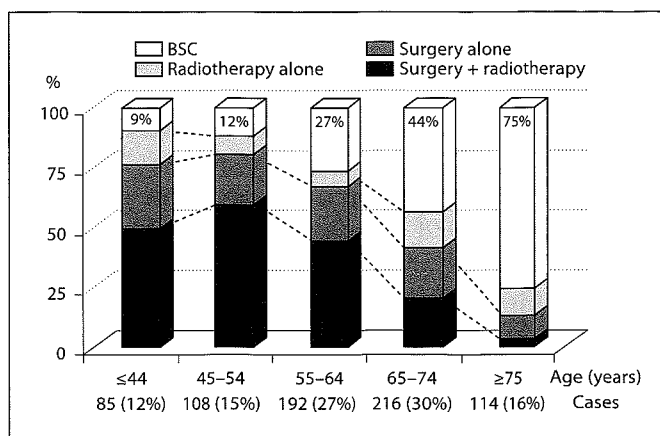


Table 1. Distribution and hazard ratios of glioblastoma patients according to treatment characteristics

	All (n = 664)		<60 years (n = 275)		≥60 years (n = 389)	
	n	HR ¹	n	HR ¹	n	HR ¹
Gender						
Male	377	1	173	1	204	1
Female	287	1.05 (0.89–1.23)	102	1.20 (0.93–1.55)	185	0.94 (0.76–1.16)
Age (years)						
<45	77	1	77	1		
45–49	52	0.81 (0.56–1.16)	52	0.81 (0.55–1.19)		
50–54	53	0.99 (0.69–1.42)	53	1.04 (0.73–1.50)		
55–59	93	1.23 (0.91–1.67)	93	1.24 (0.91–1.70)		
60–64	91	1.35 (0.99–1.85)			91	1
65–69	114	1.50 (1.11–2.04)			114	1.11 (0.84–1.48)
70–74	94	1.28 (0.92–1.78)			94	0.98 (0.72–1.34)
≥75	90	1.42 (1.01–2.02)			90	1.05 (0.76–1.46)
χ ² ₁ for trend		11.92; p < 0.001		2.83; p = 0.09		0.0; p = 0.98
Treatment						
BSC	214	1	35	1	179	1
Radiotherapy alone	66	0.42 (0.31–0.57)	19	0.28 (0.15–0.51)	47	0.52 (0.37–0.73)
Surgery alone	145	0.43 (0.34–0.54)	66	0.49 (0.31–0.77)	79	0.39 (0.29–0.52)
Surgery plus radiotherapy	239	0.17 (0.14–0.22)	155	0.15 (0.10–0.23)	84	0.18 (0.13–0.26)

Figures in parentheses are 95% CI. ¹ The model includes all the variables in the table.

(58.3 years; p = 0.039), radiotherapy alone (62.2 years; p = 0.0001) or BSC (69.2 years; p < 0.0001).

Effects of Treatments in Younger and Older Patients

In a univariate analysis, for each group of patients treated with different protocols, patients were further divided into 2 groups (<60 years old vs. ≥60 years old) for analyses of survival. Younger patients (<60 years) who were treated with surgery plus radiotherapy and those

who were treated with radiotherapy alone showed significantly longer survival than older patients (≥60 years; fig. 2). In contrast, among patients who were treated with surgery alone or those who received BSC, there was no significant difference in survival between older and younger patients (fig. 2).

Multivariate analyses adjusted for gender and treatment modality showed that older age was associated with a significantly increased hazard ratio (HR; table 1). The

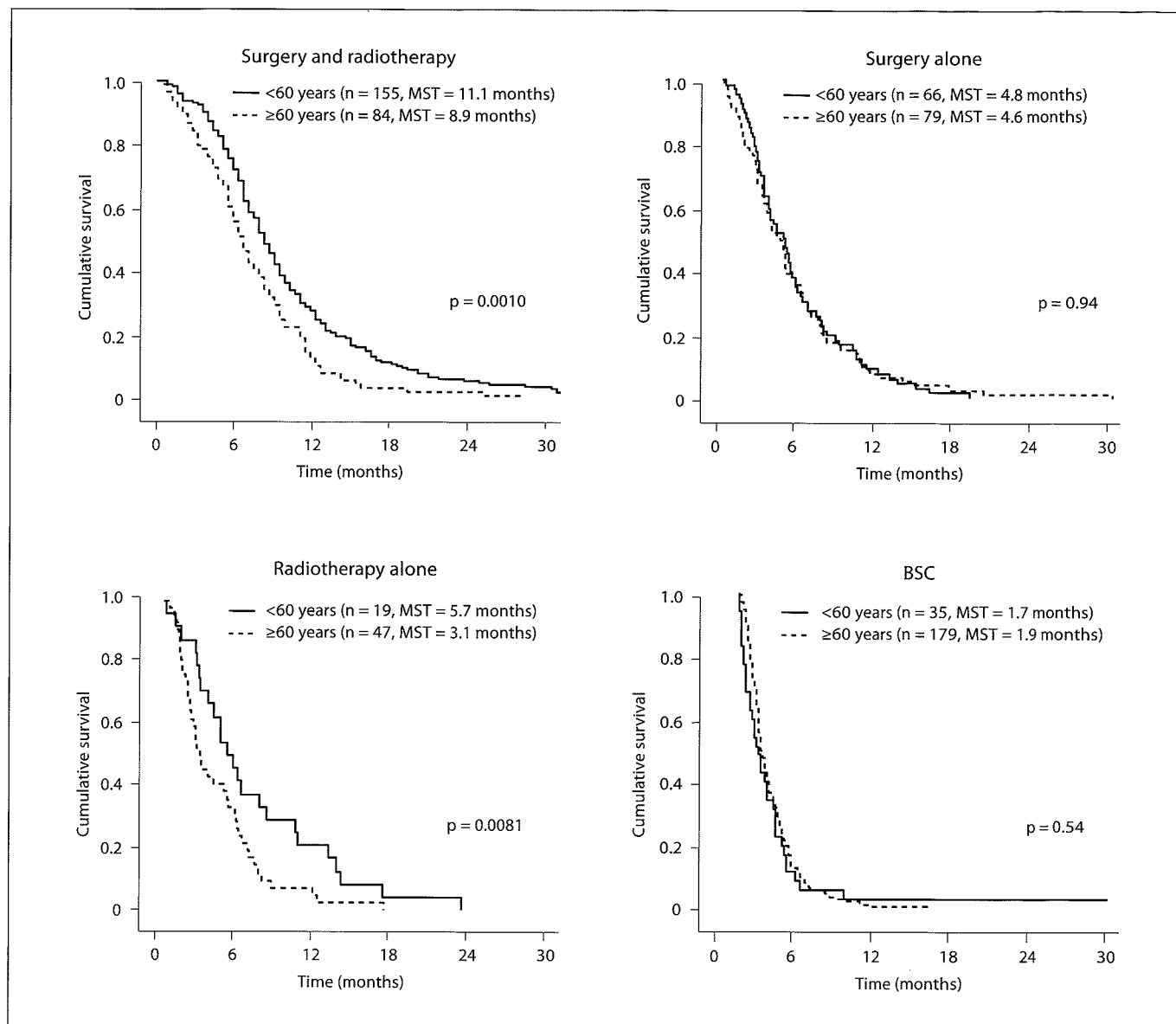


Fig. 2. In glioblastoma patients who received surgery and radiotherapy and those who received radiotherapy alone, older age (>60 years) was a significant predictive factor of poorer survival. In contrast, age is not predictive in patients who were treated with surgery alone or those treated with BSC. MST = Mean survival time.

test for linear trend was also significant ($p < 0.001$; table 1). When patients were further divided into 2 age groups (<60 years old vs. ≥ 60 years old), all 3 treatment modalities significantly improved survival in both younger and older patients, but the beneficial effect of radiotherapy alone was greater in younger patients (HR = 0.28; 95% CI: 0.15–0.51) than in older patients (HR = 0.52; 95% CI: 0.37–0.73; table 1).

Discussion

During the past decades, guidelines for the first-line therapy of glioblastoma patients have varied in different hospitals and different countries. However, there is very limited information on how patients were actually treated at the population level. The present population-based study includes glioblastoma patients diagnosed in 1980–

1994 in the Canton of Zürich, Switzerland, and, during this study period, the general policy of treating glioblastoma patients in University of Zürich and major cantonal hospitals was surgical intervention aimed at maximum tumor removal, followed by radiotherapy. Therefore, it was an unexpected finding that only 33% of patients actually received the recommended treatment. There was a striking tendency toward limited intervention and radiotherapy with advancing patient age. Of those younger than 65 years, 82% were treated either with surgery followed by radiotherapy, surgery alone or radiotherapy alone, versus 47% of patients who were 65 years or older. Only 25% of patients older than 75 years underwent surgery and/or radiotherapy, while the remaining patients were only given BSC.

Since Switzerland has health insurance coverage for virtually all citizens and easy access to specialized neurosurgery and radiotherapy centers, it is unlikely that economic factors affected the decision on diagnostic and therapeutic procedures to any significant extent. Although the present retrospective study lacks information on the performance status of patients, which is likely to have influenced treatment decisions, it is well known that in older patients, glioblastomas often cause rapid deterioration of overall clinical status [11]. Physicians therefore may have been reluctant to treat such patients with surgery and radiotherapy. Patients and their families may also have decided against surgical intervention and radiotherapy after having being informed of the limited impact on clinical outcome. The situation may be different today, as technological developments, such as functional and fiber tracking MRI, intraoperative neurofunctional monitoring and neuronavigation have rendered surgical procedures safer and more effective [12]. In a study in 2001–2005, Keime-Guibert et al. [13] reported that radiotherapy resulted in a modest improvement in survival, without reducing quality of life or cognition, of elderly patients (>70 years) with glioblastoma. Furthermore, the addition of chemotherapy has improved the chances not of a cure but at least of an extended survival period [3]. However, it remains to be shown to what extent these improvements affect the treatment decisions of glioblastoma patients on the population level.

Due to increasing life expectancy and development of sophisticated treatment procedures, the management of older glioblastoma patients may become increasingly important [14]. Since the introduction of CT and MRI, the incidence rates of brain tumors have been rather stable, with a tendency toward higher rates in highly developed, industrialized countries [15]; however, some studies sug-

gest an increase in the incidence of malignant gliomas, in particular in elderly patients [16–18].

In the present study, younger age was significantly associated with longer survival among patients who were treated with surgery plus radiotherapy and those treated with radiotherapy alone, whereas in patients treated with surgery alone or who only received BSC, overall survival was not different between younger (<60 years) and older patients (≥ 60 years; fig. 2). This finding was also supported by multivariate analyses (table 1). This suggests that surgery, radiotherapy or surgery plus radiotherapy improved survival in both younger and older patients, but that the beneficial effect of radiotherapy appeared to be significantly greater in younger than in older patients. Thus, although radiotherapy had a significant therapeutic effect in all age groups (table 1, fig. 2), the shorter survival of older glioblastoma patients appears to be at least in part due to a lesser response to radiotherapy.

It remains to be shown which genetic or epigenetic mechanisms are responsible for the increased radioresistance in glioblastomas of older patients. One study showed a correlation between epidermal growth factor receptor (EGFR) overexpression and poor radiotherapy response of glioblastoma [19], while our previous study did not show any significant difference in the frequency of several key genetic alterations (*EGFR* amplification, *TP53* mutations, *PTEN* mutations, *p16^{INK4a}* homozygous deletion, and LOH 10q) in glioblastomas that developed in different age groups [9].

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